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National Toxicology Program call for additional public comments on atrazine proposal for review for listing in the Report on Carcinogens, 12th edition

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We respectfully submit these comments on behalf the NRDC, Defenders of Wildlife, Center for Biological Diversity, TEDX, Farmworker Justice Fund, NCAMP, Beyond Pesticides, Northwest Coalition for Alternatives to Pesticides, and Rachel Carson Council. Collectively, our members represent millions of Americans dedicated to protecting worker health and safety, and the planet's wildlife and wild places, ensuring a safe and healthy environment for all living things.

We support the National Toxicology Program (NTP) when it originally announced its intent to review atrazine and twenty other agents for possible listing or changing the current listing in the 12th Report on Carcinogens (RoC) (May, 2004). This announcement was challenged under the Data Quality Act[1] by Mr. Tozzi of the Center for Regulatory Effectiveness (CRE), and various agriculture groups that represent atrazine users[2]. The Data Quality Act petition raised trivial concerns about alleged inconsistencies in NTP review procedures posted on the NTP website. However, the petition specifically took issue with the intent by NTP to review atrazine for listing in the Report on Carcinogens. The petitioners claimed that listing atrazine in the RoC would negatively impact their ability to use this toxic herbicide. Despite mounting evidence to the contrary, these same groups of atrazine users have argued to the Environmental Protection Agency (EPA) that atrazine is not harmful to human health or wildlife under currently allowed uses. In response, EPA has classified atrazine as, "not likely" a human carcinogen, and therefore not considered the carcinogenic risk that atrazine exposure may pose.

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[1] Information Quality Act Request for correction of information: RoC Procedures. Jim Tozzi, Center for Regulatory Effectiveness. June 28, 2004

[2] Kansas Corn Growers Association, Missouri Corn Growers Association, Hawaii Agriculture Research Center, Kansas Grain Sorghum Producers Association, California Citrus Mutual

In July, 2003, an independent panel of fourteen scientists, the Scientific Advisory Panel (SAP), was convened by EPA to provide advice on the health risks associated with atrazine. These scientists concluded that the carcinogenicity of atrazine had not been adequately reviewed by EPA, and a classification of "not likely" carcinogenic could not be supported by available data.[3] The SAP report concluded, it is "*the Panel's opinion that the evidence presented is inadequate to support the Agency's conclusion of atrazine as an "unlikely" cause of prostate cancer.*"[4] (italics added for emphasis)

The Scientific Advisory Panel reviewed an epidemiological study of atrazine-exposed workers in an atrazine manufacturing plant in St. Gabriel, Louisiana. This study was sponsored by the manufacturer, Syngenta. After a full review, the SAP concluded that, "given the limitations in both the study design and the analysis of the cohort study, at this time a role for atrazine as a potential cause of prostate cancer cannot be considered unlikely", and that, "the Panel could not rule out the possibility that atrazine exposure may be a contributing factor in the observed increase in prostate cancer incidence." Among the limitation in study design, the SAP noted the small sample size, insufficient statistical power, inadequate exposure information, and short follow-up time.

Importantly, the SAP expressed its frustration with EPA limiting its review of atrazine carcinogenicity to the Syngenta-sponsored epidemiology, and recommended that a full review of all studies relevant to atrazine carcinogenicity be performed:

> "The panel members expressed concern that the SAP review was limited to the epidemiologic studies of the prostate cancer findings. Partly, this concern was due to previous SAP recommendations "that the epidemiological data should be discussed as extensively as the animal data," (FIFRA Scientific Advisory Panel Meeting, June 27-29, 2000, Atrazine: Hazard and Dose Response Assessment and Characterization) and the concern that the review of the prostate cancer studies in isolation could be misleading. The June 2000 SAP report (SAP Report No. 2000-05) suggested that the epidemiologic studies of non-Hodgkin's lymphoma "were discounted even though they suggested . . .

[3] Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Characterization of Atrazine Cancer Epidemiology Data. Meeting of the FIFRA Scientific Advisory Panel. Docket Number OPP-2003-0186. July, 2003. Memorandum of transmittal of meeting minutes, issued August 29, 2003.

[4] SAP report August, 2004. ibid

adverse health effects." *The panel members recommended a broader review of these studies of other cancers, including recent studies, and that such a review could serve as the subject of a future meeting of the SAP. Further, because of the common mechanism of action of the triazines, epidemiologic studies relating to cancers and exposure to simazine and other triazines also should be included in such a review.*"[5] (italics added for emphasis)

We support the National Toxicology Program as the most appropriate scientific program to perform the broad review of all data relevant to atrazine carcinogenicity, as recommended by the EPA Scientific Advisory Panel.

We suggest that the National Toxicology Program consult with the researchers of the Agriculture Health Study for any updates and insights that may be available, to aid in their review of atrazine carcinogenicity. The National Cancer Institute evaluated cancer incidence in atrazine-exposed pesticide applicators among 53,430 participants in the Agriculture Health Study, all licensed pesticide applicators in Iowa and North Carolina. The authors reported a suggested trend for lung, bladder, non-Hodgkin's lymphoma, and multiple myeloma associated with atrazine exposure. While overall cancer incidence was not associated with atrazine exposure: non-Hodgkin lymphoma was increased about 1.5 fold above background, and multiple myeloma was increased 1.5-2 fold above background. The authors recommend further study for those tumor types for which there was a suggestion of a trend.

Animal data supports the suggested trend reported by the authors of the Agriculture Heath Study, noting a suggested association with atrazine-exposure and lymphoma incidence. Donna et al report a statistically significant increase (p-value less than 0.001) of lymphomas (6/30) in a group of 30 male] Swiss albino mice "given intraperitoneally 0.25 cc of a 2 ppm solution of atrazine for 13 times every third day to total administration of 0.26 mg of Atrazine/kg of body weight". Lymphomas arising in control animals were only 1/100. This increase in tumors among treated animals was evident after only one year of atrazine treatment.[6]

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[5] SAP report August, 2004. ibid

[6] Donna A, Betta PG, Robutti F, Bellingeri D. Carcinogenicity testing of atrazine: preliminary report on a 13-month study on male Swiss albino mice treated by intraperitoneal administration. G Ital Med Lav. 1986 May-Jul;8(3-4):119-21.

We strongly recommend that the early-life susceptibility to atrazine carcinogenicity be considered by the National Toxicology Program in its review. Published data by EPA scientists S. Fenton and L. Birnbaum demonstrate in animal studies that exposure to atrazine during development of Long Evans (LE) rats increases the risk of developing cancer later in life. LE rats were exposed in utero to atrazine, followed by challenge with the carcinogen dimethybenz[a]anthracene.[7] Atrazine-exposed pups demonstrated delayed mammary bud outgrowth, followed by an increase in multiplicity and volume of tumors after exposure to the carcinogen, compared to non-atrazine treated controls. In addition, the atrazine-exposed pups showed an increase in organ pathology, compared with controls. The authors suggest that by delaying mammary gland development, gestational atrazine exposure increases the susceptibility of the LE female to carcinogens, perhaps, by extending the period of vulnerability.[8]

A preliminary study by Syngenta Crop Protection, Inc., of atrazine administered by oral gavage to ovariectomized Rhesus monkeys reported a statistically significant decrease in serum LH in atrazine-treated monkeys. In addition, serum estradiol was greater in the treated monkeys (a significant group effect). The statistical power of the study was weakened by the loss of two animals from the atrazine-treated group (one based on body weight and one death). While the study has a high degree of variability, and is considered "inadequate" and inconclusive by EPA, the reviewers considered the report worthy of some consideration.[9]

There is evidence from multiple animal species, both sexes, and multiple rodent strains, that atrazine acts as an endocrine disruptor. Male[10] and female[11] Wistar rats displayed delayed

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[7] Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. Environ Health Perspect. 2003 Apr;111(4):389-94.

[8] Fenton SE, Davis CC. 2002. Atrazine exposure in utero increases dimethylbenz[a]anthracene-induced mammary tumor incidence in long evans offspring. Society of Toxicology Abstr., p. 185

[9] Cooper RL, Laws SC, Stoker TE. Review of oral (gavage) study on the effect of atrazine on pituitary hormone secretion of ovariectomized, estrogen-replaced female rhesus monkeys. US EPA Endocrinology Branch, Research Triangle Park. August 26, 2004

[10] Stoker TE, Laws SC, Guidici DL, Cooper RL. The effect of atrazine on puberty in male wistar rats: an evaluation in the protocol for the assessment of pubertal development and thyroid function. Toxicol Sci. 2000 Nov;58(1):50-9.

[11] Laws SC, Ferrell JM, Stoker TE, Schmid J, Cooper RL. The effects of atrazine on female wistar rats: an evaluation of the protocol for assessing pubertal development and thyroid function. Toxicol Sci. 2000 Dec;58(2):366-76.

puberty following atrazine treatment. In Fischer rats, atrazine treatment resulted in reduced sperm motility.[12] Treatment of nursing Wistar dams with atrazine suppressed suckling-induced prolactin release, leading to lateral prostate inflammation in the suckling male offspring.[13] Frogs exposed to atrazine under laboratory conditions displayed gonadal abnormalities, including hermaphroditism.[14] [15] [16] [17] We therefore suggest that the NTP include in its review available evidence in multiple strains and species of animals that atrazine causes events generally known to be associated with tumor formation, to which early life stages (in utero exposures) are especially vulnerable.

We suggest that the NTP consider both strain-specific and sex-specific responses to atrazine in its review. While both male and female Wistar rats responded to atrazine-treatment with delayed puberty, males responded at much lower treatment doses. In the female, oral gavage of 50-200 mg/kg atrazine at postnatal day 22-41 resulted in delayed vaginal opening (puberty), in a dose-dependent manner.[18] In male rats, preputial separation was significantly delayed following

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[12] Kniewald J, Jakominic M, Tomljenovic A, Simic B, Romac P, Vranesic D, Kniewald Z. Disorders of male rat reproductive tract under the influence of atrazine. J Appl Toxicol. 2000;20(1):61-8.

[13] Stoker TE, Robinette CL, Cooper RL. Maternal exposure to atrazine during lactation suppresses suckling- induced prolactin release and results in prostatitis in the adult offspring. Toxicol Sci. 1999;52(1):68-79.

[14] Tavera-Mendoza L, Ruby S, Brousseau P, Fournier M, Cyr D, Marcogliese D. Response of the amphibian tadpole Xenopus laevis to atrazine during sexual differentiation of the ovary. Environ Toxicol Chem. 2002;21(6):1264-7.

[15] Carr JA, Gentles A, Smith EE, Goleman WL, Urquidi LJ, Thuett K, Kendall RJ, Giesy JP, Gross, TS, Solomon, KR, Van Der Kraak, G. Response of larval Xenopus laevis to atrazine: Assessment of growth, metamorphosis, and gonadal and laryngeal morphology. Environ Toxicol Chem. 22: 396-405 (2003).

[16] Hayes T, Haston K, Tsui M, Hoang A, Haeffele C, Vonk A. Atrazine-Induced Hermaphroditism at 0.1 ppb in American Leopard Frogs (Rana pipiens): Laboratory and Field Evidence. Environ Health Perspect. 2003 Apr;111(4):568-75

[17] Mckoy KA, Sepulveda MS, Gross TS. Atrazine exposure and reproductive system abnormalities in field collected Bufo marinus. Abstract, 23rd Annual Meeting in North America, Soc. Environ. Toxicol. Chem., Salt Lake City, UT (2002).

[18] Laws SC, Ferrell JM, Stoker TE, Schmid J, Cooper RL. The effects of atrazine on female wistar rats: an evaluation of the protocol for assessing pubertal development and thyroid function. Toxicol Sci. 2000 Dec;58(2):366-76.

treatment with 12.5, 50, 100, 150, and 200 mg/kg atrazine administered by gavage (PND 23-53), resulting in delayed puberty.[19]

We look forward to the National Toxicology Program review of atrazine and other agents listed in the Federal Register notice, for consideration for listing in the Report on Carcinogens, 12th edition.

Thank you for consideration of these comments,

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[19] Stoker TE, Laws SC, Guidici DL, Cooper RL. The effect of atrazine on puberty in male wistar rats: an evaluation in the protocol for the assessment of pubertal development and thyroid function. Toxicol Sci. 2000 Nov;58(1):50-9.